IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al.

Application No.: 10/816,798 Art Unit 1625

Filed: April 2, 2004 Examiner: Celia C. Chang

For: NOVEL CRYSTALLINE FORM VI OF DONEPEZIL HYDROCHLORIDE AND PROCESS FOR THE PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed on September 7, 2007 for the subject application, a brief in support of the appeal is now submitted. Submission of a brief in support of the appeal in this case was due by November 7, 2007. Attached herewith is a Petition for five months extension of time (April 7, 2008). Therefore, this brief is being timely filed.

1. Real Party in Interest

The real parties in interest are Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories, Inc., assignees of the application from the inventors/appellants.

2. Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal, or which will affect or have a bearing on this appeal.

3. Status of the Claims

Claims 2-6 and 8-12 were finally rejected in an Office Action mailed on May 7, 2007, and are the subject of this appeal. Claims 1 and 7 were previously canceled.

4. Status of Amendments

In the final Office Action mailed on May 7, 2007, the Examiner objected to claims 8-12 as being in improper form. Applicants traversed. Applicants include a pertinent argument at an appropriate place herein below.

An Amendment After Final was filed on July 20, 2007, subsequent to the final rejection. No claims were amended, canceled or added. The Examiner indicated in an Advisory Action mailed August 30, 2007 that the request for consideration was considered but did not place the application in condition for allowance for reasons set forth in the record.

5. Summary of Claimed Subject Matter

The claimed subject matter encompasses crystalline form VI of donepezil hydrochloride and processes for making it.

Independent claim 2 is directed to crystalline form VI of donepezil hydrochloride having an X-ray powder diffraction pattern substantially as depicted in figure 1. (Instant specification, page 4 and Figure 1.)

The dependent claims are directed to various embodiments of the disclosed compound and processes for making it.

A copy of the appealed claims is appended hereto, beginning at page 10.

6. Grounds of Rejection to be Reviewed on Appeal

a. Whether claims 2-6 are unpatentable under 35 U.S.C. § 102(b) over Imai et al (U.S. Pat. No. 5,985,864; *Imai*).

b. Whether claims 2-6 and 8-12 are unpatentable over *Imai* in view of Doelker, *Ann. Pharm. Fr.* 60:161-176 (2002) ("*Doelker*"), Wikipedia, Article on Polymorphism, 1-2 (2006) ("*Wikipedia*"), Davidovich et al., Am. Pharm. Rev. 7:10, 12, 14, 16, 100 (2004) ("*Davidovich*"), or U.S. Pharmacopea #23 (1995) ("USP #23").

c. Whether claims 8-12 had been properly objected to under 37 CFR § 1.75(c) for being in an improper dependent form.

7. Argument

a. Rejection Under 35 U.S.C. § 102(b)

Claims 2-6 stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by *Imai*. Independent claim 2 is directed to crystalline form VI of donepezil hydrochloride having XRD substantially as in Figure 1. Claim 6 depends from claim 2, and is directed to a process for preparing crystalline form VI of donepezil hydrochloride.

According to the Examiner, Figure 3 of *Imai* discloses an X-ray powder diffraction ("XRPD") pattern substantially similar to that shown in Figure 1 of the present application on appeal. The Examiner has provided a comparison of the XRPD patterns in Exhibit I, attached with the final Office Action mailed on May 7, 2007. The Examiner also contends that Example 18 of *Imai* disclosed donepezil base in solution.

Applicants respectfully disagree.

According to the MPEP § 2131:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 638, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Imai does not disclose crystalline Form VI of donepezil hydrochloride, or a process for its preparation, having each and every limitation as set forth in the rejected claims 2-6. The XRPD pattern for *Imai*'s crystalline form III of donepezil hydrochloride, shown in Figure 3 of *Imai*, is substantially different than the XRPD pattern for crystalline form VI depicted in Figure 1 of the instant application. The Examiner's Exhibit I only strengthens this conclusion. For example, the XRPD pattern for the crystalline form VI of donepezil hydrochloride has a substantial peak at about 11.5 degrees two-theta that is clearly absent from the pattern for the crystalline form III of *Imai*. Likewise, the XRPD

pattern for the crystalline form lII of *Imai* has a substantial peak at about 6.5 degrees two-theta that is clearly absent from the pattern for crystalline form VI.

Therefore, the rejected claims 2-6 adequately distinguish the crystalline form VI from the polymorph disclosed in *Imai*, and the Examiner has failed to make a *prima facie* case for anticipation of claims 2-6 over *Imai*. *See Ex parte Havens*, Appeal No. 2001-0091 for U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2001) ("The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed [in the prior art reference] is in the [claimed] crystal form. Therefore, the examiner has not made out a *prima facie* case of anticipation by inherency").

Further, the record of this Appeal contains direct evidence that the claimed crystalline form VI of donepezil hydrochloride is different from the crystalline form III of *Imai*. Particularly, the *Imai* polymorph has a melting point of 229-231°C (*see* '864 patent, col. 7, lines 12-13), whereas the melting point of crystalline form VI is 222-225°C (*see* page 8, lines 3-4). The difference in melting points is evidence that the two polymorphs are distinct. *See Ex parte Polniaszek*, Appeal No. 2001-1805, U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("[N]otwithstanding that the claimed compound has the same formula as [the prior art compound], the examiner has not established that [the prior art compound] suggests appellants' specifically claimed polymorph. This is clearly demonstrated by the different melting points for the two compounds").

Applicants also note that claim 6, directed to a process for preparing crystalline form VI, recites reacting the donepezil/ethanol solution of step (a) with an HCl source at 25 to 35°C. In contrast, Example 18 of *Imai* performs an HCl reaction in an ice bath (*see* '864 patent, col. 15, lines 52-53). This provides another basis for the novelty of claim 6, in addition to distinctions related to independent claim 2.

To establish a *prima facie* case of inherent anticipation, the Examiner must show scientific rationale or objective evidence tending to show inherency. *See* MPEP § 2112. Only then the burden will shift to the Applicants to disprove the inherency. *See id.*, *citing*, *Ex Parte Skinner*, 2 USPQ2d (BNA) 1788 (BPAI 1986).

Applicants make reference to the recent decision of the Board of Patent Appeal and Interferences in *Ex Parte Buchi*, 2007 WL 2745815 (September 6, 2007). In the present case, as in *Buchi* and *Havens*, the evidence adduced by the Examiner does not justify shifting of the burden. While *Imai* discloses a crystalline form of donepezil hydrochloride, the rejected claims recite a particular polymorph, namely form VI. As in *Buchi* and *Havens*, the Examiner did not provide a reason why the burden should shift to the applicants, and therefore did not set forth a *prima facie* case of inherency.

Accordingly, Applicants submit that claims 2-6 are not anticipated by *Imai*, and the rejection should not be sustained.

b. Rejection Under 35 U.S.C. § 103(a)

Claims 2-6 and 8-12 stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over *Imai* in view of *Doelker*, *Wikipedia*, *Davidovich*, or USP #23. According to the Examiner, *Imai* discloses the anticipatory product as claimed in claims 2-5 made by the process of claim 6. The differences between dependent claims 8-12 wherein variations of solvent systems was employed in the process of crystal preparation is said to be generically taught by *Imai*. Thus, according to the Examiner one having ordinary skill in the art in possession of *Imai* is in possession of the instantly claimed variations.

Applicants respectfully disagree.

According to MPEP § 706.02(j):

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed above with respect to the § 102 rejection, Form VI, claimed in the present application, and Form III of *Imai* are clearly distinct polymorphic forms. There is no teaching or suggestion in *Imai* that donepezil hydrochloride may exist in form VI, and no reason is provided to modify the polymorph of *Imai*. This alone is enough to overcome the Examiner's obviousness rejection. *See Ex parte Havens*, Appeal No. 2001-0091 for U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . . The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") (emphasis added).

The proper test for obviousness is not whether the possible existence of additional polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular polymorph, *i.e.*, the crystalline form VI of donepezil hydrochloride disclosed and claimed in the instant application:

> The law of § 103 requires quite a different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

See Bristol-Myers Co. v. U.S. Int'l Trade Comm'n, 892 F.2d 1050, 1989 WL 147230 (Fed. Cir. Dec. 8, 1989) (unpublished decision) (emphasis added).

At most, the references cited by the Examiner suggest the possibility of additional polymorphs of donepezil hydrochloride. The Examiner has pointed to nothing in the cited references, either alone or in combination, which would suggest to one skilled in the art the particular form VI of donepezil hydrochloride disclosed and claimed in the instant application, or a method for its preparation. *See Ex parte Polniaszek*, Appeal No. 2001-1805, U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("The prior art relied upon by the examiner does not teach this specific polymorph as claimed by the appellants. The Examiner failed to demonstrate that the prior art even recognized

that the claimed compound exists in different polymorphic forms, or that there is a known or obvious way to manufacture the specific polymorphic form claimed").

Recent decisions of the United States Court of Appeals for the Federal Circuit and Board of Patent Appeals and Interferences continue to require, as a basis of finding obviousness, a reason for one skilled in the art to modify the prior art in the direction of claimed invention. *See, e.g., Ortho McNeil Pharm., Inc. v. Mylan Laboratories, Inc.*, Slip Opinion, at p. 11 (Fed. Cir. March 31, 2008) ("A flexible TSM test remain a primary guarantor against non-statutory hindsight analysis"); *In re Translogic Tech, Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *Ex Parte Buchi*, 2007 WL 2745815 (BPAI 2007).

In *Buchi*, the claims to specific polymorphs were rejected over disclosure of a known crystalline form. 2007 WL 2745815, at 2. The Examiner cited Cheronis as a secondary reference to show that use of re-crystallization is well know in the art and finding obviousness of the basis of combining Cheronis with a primary reference that taught a crystalline solid. In other words, the Examiner in *Buchi* argued that since re-crystallization is known, an artisan would employ it to arrive at the claimed polymorph. The Board rejected this reasoning, stating that while one would be expected to purify by crystallization, "that would not necessarily lead to the claimed crystalline forms." *Id.* at 5. This is no different than the situation in the present appeal. In effect, the Board of Patent Appeals and Interferences did not support the automatic *prima facie* obviousness standard. *See id.* In fact, it is clear that the legal requirements for *prima facie* obviousness (*e.g.*, disclosure of all claim elements and reasonable of expectation of success) are the law with respect to claims for polymorphic forms.

Accordingly, Applicants submit that the rejected claims are not *prima facie* obvious over *Imai* in view of *Doelker*, *Wikipedia*, *Davidovich* or USP #23, and this rejection should not be sustained.

c. Objection to Claims 8-12

Claims 8-12 stand objected to under 37 CFR § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. According to the Examiner, the dependent claims are drawn to scope of

"comprising" alcohol or ether, which is broadening of the base claim wherein only alcohol or ether was the solvent.

Applicants respectfully disagree.

Claims 8-12 are directed to a process for preparing the crystalline donepezil HCl form VI of claim 2. Contrary to the Examiner's position, claim 2 does not recite alcohol or ether, or any solvent for that matter. Because claims 8-12 specify how the crystalline donepezil HCl form VI of claim 2 is prepared, they do limit the subject matter of the base claim, and thus are proper dependent claims. *See* MPEP § 608.01(n), part III.

Accordingly, Applicants submit that claims 8-12 meet the requirements of 37 CFR § 1.75(c), and the objection should not be sustained.

However, if the Board of Patent Appeals and Interferences decides that the subject matter is more suitable to resolution in the course of ordinary patent prosecution, Applicants would respectfully agree and resolve this objection after the decision of the Board on the grounds a. and b.

CONCLUSION

Applicants submit that claims 2-6 and 8-12 meet the requirements for patentablility under §§ 102 and 103. Accordingly, reversal of the Examiner's rejections is appropriate and is respectfully solicited.

Respectfully submitted,

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CLAIMS APPENDIX

2. Crystalline form VI of Donepezil hydrochloride having an X-ray powder diffraction pattern substantially as depicted in Figure 1.

3. Cystalline Form VI of Donepezil hydrochloride according to claim 2 having an infrared spectrum substantially as depicted in Figure 2.

4. Crystalline form VI of Donepezil hydrochloride according to claim 2 having a thermogravimetric analysis thermogram substantially in accordance with Figure (3).

5. Crystalline form VI of donepezil hydrochloride according to claim 2 having a Differential Scanning Calorimetry thermogram substantially as depicted in Figure 4.

6. A process for preparing the crystalline form VI of Donepezil hydrochloride of claim 2, which comprises:

a. dissolution of Donepezil free base in a suitable alcoholic solvent at 60 to 65°C;

b. reacting the solution of step (a) with an HCL source at 25 to 35°C to afford Donepezil hydrochloride;

c. diluting the reaction mass of step (b) with an ether solvent;

d. stirring the reaction mass of step (c) at 25 to 35°C for a period of 0.5 to 10 hours;

e. filtration of the separated solid from step (d) by conventional methods; and

f. drying the crystalline solid from step (e) at 50-55°C for a period of 5-8 hours under reduced pressure to afford crystalline form VI of Donepezil hydrochloride.

8. A process for preparing crystalline form VI of donepezil hydrochloride of claim 2, comprising combining a solution comprising donepezil hydrochloride and an alcohol with an ether, and separating donepezil hydrochloride form VI.

9. The process of claim 8, wherein an alcohol comprises methanol, ethanol, propanol, or butanol.

10. The process of claim 8, wherein an alcohol comprises methanol.

11. The process of claim 8, wherein an ether comprises diethyl ether, methyl tert-butyl ether, or diisopropyl ether.

12. The process of claim 8, wherein an ether comprises diisopropyl ether.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.